Dura
PHARMACEUTICALS

July 14, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

REF: Docket No. 99D-0674

Reference is made to the draft guidance for industry, "INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products Chemistry, Manufacturing, and Controls Content and Format" Docket Number 99D-0674, published in the Federal Register on February 16, 1999. Dura Pharmaceuticals Inc. (Dura) is providing the following comments on the recommendations included in this guidance.

Section I. Introduction
Lines 20-23

Dura strongly supports the publication of this guidance and agrees that the goals of the guidance should be to facilitate drug discovery and development and should focus on the data to assess the safety as well as the quality of the proposed clinical studies from the chemistry, manufacturing, and controls (CMC) and microbiology perspective. Dura does not agree that this guidance will in fact expedite the entry of new drugs into the marketplace. The goal to expedite the entry of new drugs into the marketplace, while still important, contradicts the intent of this guidance, which is to support safety and quality. The new drug product application (NDA) describes the proposed-marketed product for which safety has been demonstrated in clinical studies. The CMC information for a new drug application is much more extensive than that required to demonstrate safety and quality in a clinical study. It is not clear how this guidance would expedite entry of new drugs into the marketplace.

Section III. Phase 2
A. Drug Substance
3. Synthesis/Method of Manufacture and Controls
Lines 157-160

Clarification is requested for the phrase "sponsors should document that the manufacturing process is controlled at predetermined points". Dura would like to understand the use of the phrase "predetermined points" versus "in-process controls" in this section of the guidance.

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4. Reference Standard
Lines 174-176

Dura is requesting identification of the type of calibration information the Agency is expecting for the phrase, "Where a recognized national or international standard (primary standard) is available, the manufacturer's reference material and/or working standard should be 'calibrated' against this standard."

7. Stability
Lines 208-210

Clarification is requested for "significant changes" for which stability-indicating analytical procedures are expected to detect in the quality of the drug substance.

Section III. Phase 2
B. Drug Product
1. Component/Composition/Batch Formula
Lines 235-237

Clarification is requested for "similar" where the guidance states that the formulation for certain drug products delivered by devices (e.g., metered dose inhalers (MDIs), dry powder inhalers (DPIs), nasal sprays) should be similar to that intended for the marketed drug product.

5. Specification
Lines 281-282

Clarification is requested on the type of validation that is considered supporting of analytical procedures used in phase 2 studies.

7. Stability
Lines 302-304

Clarification is requested for the term "representative" material. Dura would like to understand the difference, if any, between representative material and supporting material for generating stability data to support clinical studies. The guidance states that all available stability data for clinical material used in phase 1 study should be provided in phase 2. Dura recommends that specific stability data requirements be included for clinical studies initiated at phase 2.

Section IV. Phase 3/Pivotal Study
B. Drug Product
1. Components, Composition, and Batch Formula
Lines 460-462

Clarification is requested for "similar" where the guidance states that the formulation for certain drug products delivered by devices (e.g., metered dose inhalers (MDIs), dry powder inhalers (DPIs), nasal sprays) should be similar to that intended for the marketed drug product. Dura is also requesting that the type of formulation changes allowed from phase 2 to phase 3 and from phase 3 to marketed product be clearly identified specifically with regard to dry powder formulations.

5. Specification
Lines 508-509

Clarification is requested for the type and amount of "appropriate" validation information for supporting phase 3 studies. Clarification is also requested for the use of the term "supportive" in lines 281-282 versus "appropriate" in lines 508-509. Dura recommends that validation information for phase 3 be limited to a description of the parameters evaluated and that specific detail, including data, be included in the NDA as required by 21 CFR 314.50. Dura also recommends that specific phase related validation parameters be identified in this guidance.

7. Stability
Lines 532-534

Clarification is requested for the term "capability" of the analytical procedure referenced for one-time stress studies. Dura would like to understand how the term and requirements to demonstrate "capability" differ from "validation" of analytical procedures.

Please contact me at (619) 785-6341 with any questions with regard to the above comments.

Sincerely,

Darlene Rosario

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Director, Regulatory Affairs
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